Remarks

Claims 13-15 and 17-28 are currently pending. Claims 13-15 and 17-28 stand rejected under 35 U.S.C. § 103(a).

Applicants have added new Claims 29-31. Support for these amendments can be found throughout the specification. Specifically, support for Claim 29 is found at page 7, lines 9-15. Support for Claim 30 is found at page 5, lines 24-25 and page 7, lines 1-3. Support for Claim 31 is found at page 5, lines 30-36. These amendments add no new matter.

Rejection of Claims 1, 19, and 20 under 35 U.S.C. § 103(a)

Claims 13-15 and 17-28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hirahara, U.S. Patent 5,084,273 (Hirahara) in view of Mochida Pharmaceutical Co. Ltd., JP 08-301786 (Takahashi *et al.*). The current and previous office actions acknowledge that Hirahara in view of Takahashi *et al.* does not provide the claimed weight to weight ratio of about 1 part activated protein C (aPC) to between about 5 to7 parts bulking agent. The rejection of record states that the ratio of aPC to bulking agent is a result-effective parameter which was routinely optimized by one of ordinary skill in the art at the time of the invention. The current rejection additionally states that the claims are not commensurate with the disclosure since Applicants' specification does not disclose that this ratio is associated with any particular result. Applicants respectfully disagree as detailed below and request withdrawal of the rejection.

At the outset, Applicants respectfully assert that the rejection fails to set forth a *prima facie* case of obviousness. To establish a *prima facie* case, the rejection must show 1) some suggestion or motivation to modify the reference or to combine reference teachings *(In re Fine,* 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention *(Amgen, Inc. v. Chugai Pharmaceutical Co.,* 927 F.2d 1200 (Fed. Cir. 1991)); and 3) the prior art reference or combination of references must teach or suggest all limitations of the claims *(In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991)). Applicants assert that the rejection does not meet each of the required burdens of showing motivation to modify the references and that the combination of prior art references teach or suggest all limitations of the claims.

The present invention claims a method of treatment in which a patient is administered a lyophilized formulation comprising a weight to weight ratio of about 1 part activated protein C to between 5 to 7 parts bulking agent. As acknowledged in the current and

previous rejections, this ratio is not taught by the prior art. Specifically, the composition of Hirahara contains an aPC to bulking agent ratio of 1:67, while the compositions of Takahashi *et al.* contain a ratio of 1:2.5 (10 mg aPC:25 mg mannitol, Application Example 1) or 1:0.5 (50 mg aPC:25 mg mannitol, Application Example 2). As described below, Hirahara in view of Takahashi *et al.* does not provide motivation to modify the ratios taught therein toward deriving the present invention, nor do these references provide basis for obtaining the limitations of the claimed invention by routine optimization of a result-effective parameter.

The previous rejection of record states that in the compositions of Hirahara, the ratio can vary widely. More importantly, that rejection states that manipulation of this ratio is a result-effective parameter which was, at the time of Applicant's invention, routinely optimized as evidenced by the wide range of suitable concentrations of aPC in the therapeutic compositions disclosed in Hirahara. Applicants first point out that Hirahara does not disclose a wide range of aPC concentrations in the therapeutic compositions (preparations) disclosed therein. Rather, Hirahara only provides examples of lyophilized preparations, i.e. formulations, containing 1.5 mg protein C or aPC and 100 mg mannitol (see Examples 1 and 2, column 4, lines 36-51 of Hirahara). Hirahara does state in column 3, lines 29-35 that

> Protein C as an active ingredient is present in the carrier at a concentration in the range of about 2 μg/ml to 20 μg/ml, AT III in the rage of 140-300 μg/ml, and heparin in the range of 0.1-1.0 usp unit/ml. The total amount of protein in the active ingredient to be given per dose is in the range of 5 mg to 1 g for an adult weighing 60 kg. (emphasis added)

Hirahara therefore provides that the concentration of protein C as an active ingredient may vary in the carrier and/or that the amount of protein C can vary per dose. The use of the term "carrier" by Hirahara refers to the solution delivered to the patient after reconstitution of lyophilized protein C into solution. While Hirahara teaches that the concentration of protein C may vary in the carrier, nowhere does Hirahara teach or suggest that the ratio of protein C or aPC to mannitol can vary in the lyophilized preparation.

Likewise, in teaching that the amount of protein C or aPC can vary per dose, Hirahara makes no mention or suggestion of variation of protein C or aPC per lyophilized preparation. Hirahara clearly makes a distinction between a dose and a preparation. As taught by Hirahara in column 3, lines 15-27:

> In preparing the injectable pharmaceutical preparation, a pH-adjusting agent, a buffering agent, a stabilizer, an agent for effecting isotonicity and the like may be added to the active ingredients. Lyophilization may further be applied by conventional procedures to prepare freeze-dried injectable preparations. For example, one or more additives such as mannitol, sucrose,

> lactose, maltose, glucose, amino acids, and albumin may be added to the active ingredients; the mixture is dissolved in water, and the solution is divided into vials or ampules, which are then freeze-dried and tightly sealed to prepare the preparation for intravenous injection. (emphasis added)

As acknowledged in the rejection, the examples of Hirahara disclose lyophilized 10 ml preparations containing 1.5 mg of protein C or aPC. In view of the above-captioned teaching by Hirahara, the examples refer to a preparation of protein C or aPC and other components in a volume of 10 ml, which is then lyophilized. This preparation containing 1.5 mg of aPC may not be regarded as a dose, as indicated in the current rejection. Rather, this lyophilized preparation could be reconstituted in a carrier to deliver a dose of protein C or aPC as an active ingredient. Hirahara clearly teaches a dose of 5 mg to 1 g protein C or aPC for a 60 kg adult, and does not teach or suggest a dose of 1.5 mg protein C or aPC.

This dosage range of 5 mg to 1 g protein C or aPC would be obtained by delivering to the patient an appropriate volume of carrier containing the protein reconstituted from an appropriate number of lyophilized preparations. As captioned above, Hirahara clearly states that a carrier contains about 2 μg/ml to 20 μg/ml protein C or aPC. Following the teaching of Hirahara a dose of 7.5 mg could be achieved, for example, by reconstituting 5 vials of 10 ml lyophilized preparations, each containing 1.5 mg of aPC, in a total carrier volume of 375 ml, and then administering this solution of 20 μg/ml aPC active ingredient to the patient. Hirahara therefore makes a distinction between a dose and a preparation, while providing for variation in both the concentration of protein C or aPC in the carrier, and the amount of protein C or aPC in a dose. Nowhere does Hirahara teach or suggest that the ratio of protein C or aPC to bulking agent may vary in the lyophilized preparations taught therein.

Applicants further point out that even if Hirahara were to teach a range of aPC:bulking agent ratios (which Hirahara does not), manipulation of this ratio was not a result-effective parameter which a skilled artisan would have routinely optimized at the time of Applicants' invention. Before the determination of a parameter can be characterized as routine experimentation, the parameter must first be recognized as result-effective variable, i.e., a variable that achieves a recognized result. See M.P.E.P. § 2144.05 II.B.; *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Nowhere does Hirahara teach, suggest, or recognize that the ratio of aPC:bulking agent is or may be a variable that effects the stability aPC. Likewise, the teachings of Takahashi *et al.*, which include use of aPC:bulking agent ratios of 1:2.5 and 1:0.5, do not teach or suggest that the aPC:bulking agent ratio is or may be a result-effective variable in the stability of aPC in the formulations taught therein. If

anything, Takahashi *et al.* teaches away from the aPC:bulking agent ratio as a result-effective variable, since Takahashi *et al.* uses the same amount of mannitol in Application Examples 1 and 2 despite having a 5-fold difference in the amount of aPC between Example 1 (10 mg aPC) and Example 2 (50 mg aPC). Accordingly, Hirahara in view of Takahashi *et al.* would not have rendered the aPC:bulking agent ratio utilized in the methods of the present invention obvious as a result-effective variable that could be obtained by routine experimentation.

In view of the lack of Hirahara and Takahashi *et al.* to teach or suggest that the ratio of aPC:bulking agent was a result-effective parameter, one of skill in the art would not have been motivated to derive the present invention from Hirahara and Takahashi *et al.* In addition, Hirahara nor Takahashi *et al.* do not provide any other rationale which would have suggested to or motivated one of skill in the art to modify those references toward deriving the present invention.

Moreover, the autodegradation of aPC that is minimized in the formulations administered in the present invention was not previously known. Neither Hirahara nor Takahashi *et al.* are directed to formulation conditions that reduce aPC autodegradation. Instead, Hirahara teaches the development of more effective anticoagulants that inhibit both the activation process and thrombin activity by using aPC in combination with heparin and/or AT III. Takahashi *et al.* focuses on aPC as a preventative and curative drug for resorptive bone disease. The references are silent regarding whether lyophilization improves or exacerbates the autodegradation of aPC, let alone making any mention of effect of the aPC to bulking agent ratio on the protein stability. Solving aPC autodegradation problems by lyophilization employing particular amounts of aPC and bulking agent would not be obvious from reading either Hirahara or Takahashi *et al.* Accordingly, the rejection over Hirahara in view of Takahashi *et al.* fails to demonstrate some suggestion or motivation to modify the teachings of the references, and therefore does not meet the burden of a *prima facie* case of obviousness.

In addition, the rejection does not meet the *prima facie* case requirement of teaching or suggesting all of the claim limitations. As indicated above, the current and previous rejections acknowledge that Hirahara in view of Takahashi *et al.* do not specifically disclose the aPC:bulking agent ratios of the formulations employed in the methods of the claimed invention. In addition, for the reasons provided above, the aPC:bulking agent ratio was not a result-effective variable that one of skill in the art would have obtained through routine experimentation at the time of the invention. Thus, Hirahara in view of Takahashi *et al.* fails

to teach or suggest all of the limitations of the claimed invention. The present invention therefore is not obvious over Hirahara in view of Takahashi *et al.*

The present office action states that the dosing regime of claim 18 does not distinguish the claimed invention over Hirahara. The basis for this conclusion is that infusion of aPC for one to two and half hours in a 60 kg patient would result in the equivalent amount of aPC in one 10 ml preparation according to Hirahara. As explained above, Hirahara does not provide for a 1.5 mg dose. However, even if Hirahara did provide for such a dose, Hirahara provides no indication of the time over which such a dose (or the 5 mg to 1 g doses actually taught therein) should be administered. Hirahara makes no mention or suggestion of a rate at which a concentration of protein C or aPC is administered to a patient. Therefore, Hirahara does not teach all of the limitations of claim 18. The dosing regime of claim 18 is therefore both distinguished and non-obvious over Hirahara.

The present office action states within the rejection under 35 U.S.C. § 103(a) that the claims of the present invention are not commensurate in scope with the disclosure. In particular, it is asserted that by not testing different ratios of aPC:bulking agent, Applicants have not demonstrated that this preferred ratio imparts stability to solutions of aPC. Applicants respectfully submit this assertion is not a basis for rejection under 35 U.S.C. § 103(a). Nonetheless, Applicants wish to point out that the claims are commensurate in scope with the disclosure. The present application thereby fulfills the requirements of 35 U.S.C. § 112. While the specification does not provide examples in which different ratios of aPC:bulking agent are tested, Applicants have unequivocally demonstrated that the claimed ratio of aPC to bulking agent imparts stability to solutions of aPC used in the methods of the present invention. As demonstrated in Example 2, at pages 15 to 20 of the specification, aPC in formulations containing mannitol, trehalose, raffinose, or sucrose at a ratio of 1 part aPC to 6 parts bulking agent had increased chemical and physical stability when compared to aPC in a formulation without a bulking agent.

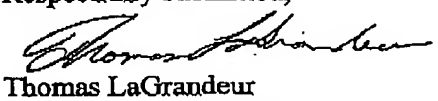
In view of the above, Applicants respectfully submit that the claimed invention, including pending claims 13-15, 17-28 as well as new claims 29-31, is not obvious over Hirahara in view of Takahashi *et al.* Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments which place the application in condition for

allowance. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,



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